Gastrointestinal mucosal damage in COVID-19 patients undergoing endoscopy: an international multicentre study.

Supplementary Table 1: Centres and Relative Case contributions

Centre	Number of included cases
ASST Papa Giovanni XXIII, Bergamo, Italy	18
IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy.	14
University of Bologna and Sant'Orsola Malpighi Hospital, Bologna, Italy	12
Hospital Casa de Saude de Santos. Santos. Brazil.	11
Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Università Cattolica del Sacro Cuore, Rome, Italy	10
University Hospitals Leuven, Belgium	9
Yale University School of Medicine, New Haven, CT, USA	9
Robert Wood Johnson Medical School Rutgers University, New Brunswick, United States	7
Sant'Andrea Hospital, Sapienza University of Rome, Italy	6
San Matteo Hospital Foundation, University of Pavia, Italy	3
University of Padua, Italy	3
Newcastle upon Tyne hospitals NHS Trust, United Kingdom	3
University Hospital of Santiago de Compostela. Health Research Institute of Santiago de Compostela (IDIS), Spain	3
Imeldaziekenhuis, Bonheiden, Belgium	3
National and Kapodistrian University of Athens, "Attikon" University General Hospital, Athens, Greece	2
Ospedale Sandro Pertini, Rome, Italy	1

Supplementary Statement 1: Inclusion and Exclusion criteria

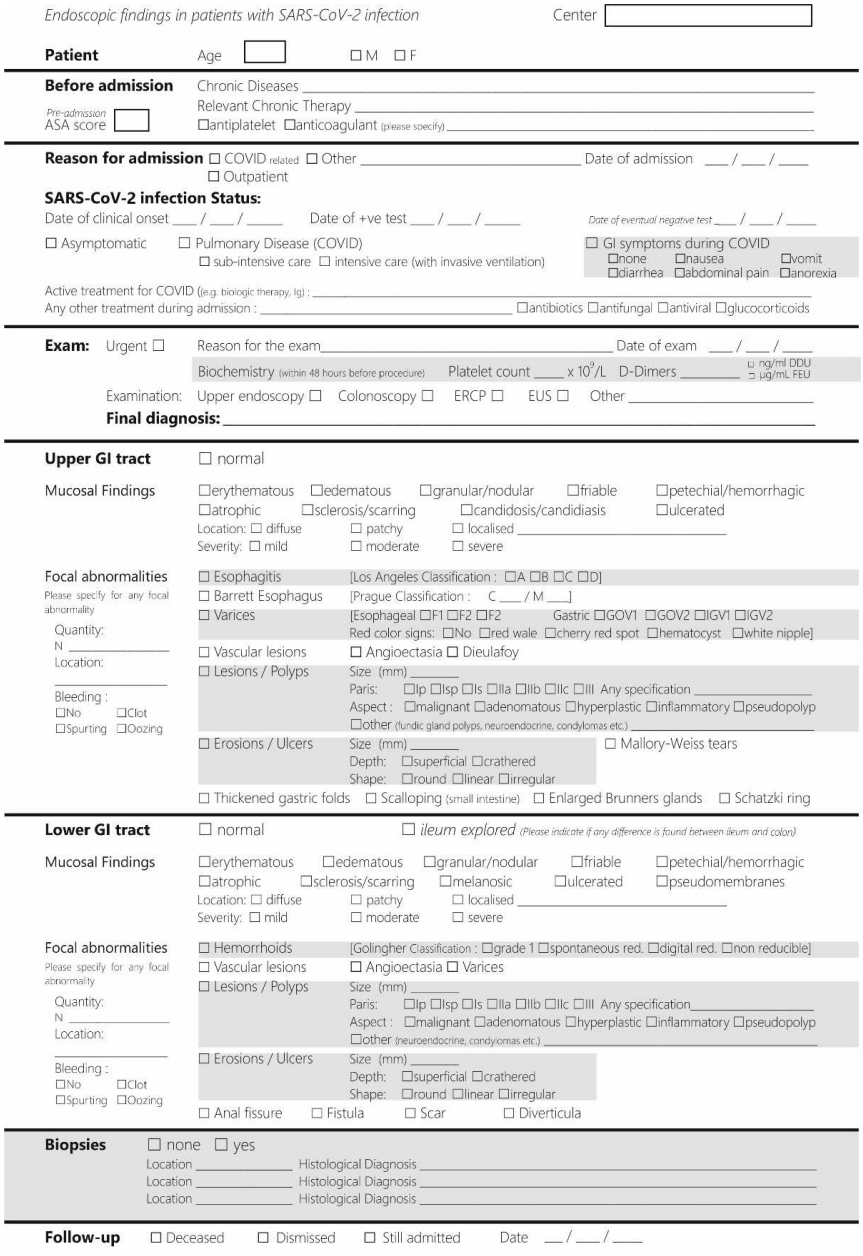
Inclusion criteria were:

1. Patients ≥ 18 years old
2. SARS-CoV-2 infection confirmed by real-time reverse-transcriptase polymerase chain reaction (PCR) identification of RNA according to WHO-approved methods[1]
3. Patients undergoing an endoscopy examination allowing direct visualization of upper or lower GI tract, including endoscopic ultrasound (EUS) and Endoscopic Retrograde Cholangio-Pancreatography (ERCP) when the endoscopist could reasonably exclude upper GI damage.

Exclusion criteria were:

1. Unclear infection status
2. Endoscopic examinations executed before COVID-19 clinical onset or positive detection test
3. Negative SARS-CoV-2 detection test at the time of endoscopic examination following a previously documented infection (i.e. recovery with viral elimination).

Supplementary Figure 1: Case Report Form



Endoscopic findings in patients with SARS-CoV-2 infection Center

Patient Age ☐ M ☐ F

Before admission Chronic Diseases
Relevant Chronic Therapy
Pre-admission ASA score ☐antiplatelet ☐anticoagulant (please specify)

Reason for admission ☐ COVID related ☐ Other Date of admission ___ / ___ / ____
☐ Outpatient

SARS-CoV-2 infection Status:
Date of clinical onset ___ / ___ / ____ Date of +ve test ___ / ___ / ____ *Date of eventual negative test* ___ / ___ / ____
☐ Asymptomatic ☐ Pulmonary Disease (COVID)
☐ sub-intensive care ☐ intensive care (with invasive ventilation)
☐ GI symptoms during COVID
☐none ☐nausea ☐vomit
☐diarrhea ☐abdominal pain ☐anorexia
Active treatment for COVID (e.g. biologic therapy, Ig) :
Any other treatment during admission : ☐antibiotics ☐antifungal ☐antiviral ☐glucocorticoids

Exam: Urgent ☐ Reason for the exam Date of exam ___ / ___ / ____
Biochemistry (within 48 hours before procedure) Platelet count ____ x 10^9/L D-Dimers ____ ☐ ng/ml DDU ☐ µg/mL FEU
Examination: Upper endoscopy ☐ Colonoscopy ☐ ERCP ☐ EUS ☐ Other
Final diagnosis:

Upper GI tract ☐ normal

Mucosal Findings ☐erythematous ☐edematous ☐granular/nodular ☐friable ☐petechial/hemorrhagic ☐atrophic ☐sclerosis/scarring ☐candidosis/candidiasis ☐ulcerated
Location: ☐ diffuse ☐ patchy ☐ localised
Severity: ☐ mild ☐ moderate ☐ severe

Focal abnormalities
Please specify for any focal abnormality
Quantity: N
Location:
Bleeding : ☐No ☐Clot ☐Spurting ☐Oozing
☐ Esophagitis [Los Angeles Classification : ☐A ☐B ☐C ☐D]
☐ Barrett Esophagus [Prague Classification : C ___ / M ___]
☐ Varices [Esophageal ☐F1 ☐F2 ☐F2 Gastric ☐GOV1 ☐GOV2 ☐IGV1 ☐IGV2
Red color signs: ☐No ☐red wale ☐cherry red spot ☐hematocyst ☐white nipple]
☐ Vascular lesions ☐ Angioectasia ☐ Dieulafoy
☐ Lesions / Polyps Size (mm)
Paris: ☐Ip ☐Isp ☐Is ☐IIa ☐IIb ☐IIc ☐III Any specification
Aspect : ☐malignant ☐adenomatous ☐hyperplastic ☐inflammatory ☐pseudopolyp
☐other (fundic gland polyps, neuroendocrine, condylomas etc.)
☐ Erosions / Ulcers Size (mm)
Depth: ☐superficial ☐crathered
Shape: ☐round ☐linear ☐irregular
☐ Mallory-Weiss tears
☐ Thickened gastric folds ☐ Scalloping (small intestine) ☐ Enlarged Brunners glands ☐ Schatzki ring

Lower GI tract ☐ normal ☐ *Ileum explored* (Please indicate if any difference is found between ileum and colon)

Mucosal Findings ☐erythematous ☐edematous ☐granular/nodular ☐friable ☐petechial/hemorrhagic ☐atrophic ☐sclerosis/scarring ☐melanosic ☐ulcerated ☐pseudomembranes
Location: ☐ diffuse ☐ patchy ☐ localised
Severity: ☐ mild ☐ moderate ☐ severe

Focal abnormalities
Please specify for any focal abnormality
Quantity: N
Location:
Bleeding : ☐No ☐Clot ☐Spurting ☐Oozing
☐ Hemorrhoids [Golingher Classification : ☐grade 1 ☐spontaneous red. ☐digital red. ☐non reducible]
☐ Vascular lesions ☐ Angioectasia ☐ Varices
☐ Lesions / Polyps Size (mm)
Paris: ☐Ip ☐Isp ☐Is ☐IIa ☐IIb ☐IIc ☐III Any specification
Aspect : ☐malignant ☐adenomatous ☐hyperplastic ☐inflammatory ☐pseudopolyp
☐other (neuroendocrine, condylomas etc.)
☐ Erosions / Ulcers Size (mm)
Depth: ☐superficial ☐crathered
Shape: ☐round ☐linear ☐irregular
☐ Anal fissure ☐ Fistula ☐ Scar ☐ Diverticula

Biopsies ☐ none ☐ yes
Location Histological Diagnosis
Location Histological Diagnosis
Location Histological Diagnosis

Follow-up ☐ Deceased ☐ Dismissed ☐ Still admitted Date ___ / ___ / ____

Supplementary Statement 2: Variables

The following variables were recorded:

1) patients' characteristics [age, sex, American Society of Anaesthesiologists (ASA) classification of pre-admission physical status[2]]
2) previous medical history [comorbidities as reported by the referring endoscopist; relevant chronic therapy; specific assessment of antiplatelet and anticoagulation at admission]
3) COVID-19-related variables [date of symptoms onset; date of positive or negative PCR; admission regimen (Intensive Care Units (ICU), non-intensive Units (NIU), not admitted (Outpatient)); pharmacologic treatments during admission (antiviral therapy, antibiotics or antifungals, biologic therapy, hydroxychloroquine, steroids and anticoagulation)[3]
4) D-Dimer values (ng/mL D-Dimer Units) and Platelet count (× 10^9/L) within 48 hours before procedure as possible biochemical markers of intravascular disseminated coagulation[4] (platelet count of patients with known liver cirrhosis was neglected)
5) Patients-reported GI symptoms [diarrhoea, vomiting, nausea, abdominal pain, anorexia)][5] unrelated to previous or concomitant conditions [symptoms of patients admitted for COVID-19-unrelated abdominal diseases (e.g. acute pancreatitis, cholangitis) were neglected];
6) endoscopy-related variables [urgent or not; indication (Upper GI (UGI) bleeding, Lower GI (LGI) bleeding, Symptoms, Placement of devices for nutritional support (e.g. percutaneous Gastrostomy or Naso-Duodenal tube)); timing of endoscopic examination with respect to SARS-CoV-2 onset (Onset-to-Endoscopy time) and the day of hospital admission (Admission-to-Endoscopy time)];
7) endoscopy findings recorded according with the Minimal Standard Terminology (MST) for Gastrointestinal Endoscopy published by the World Endoscopy Organization[6] (see Supplementary Figure 1);
8) Histopathology, when biopsies were taken as clinically indicated

9) Overall mortality

References

1. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human caseshttps://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117 (accessed 26 April 2020).

2. ASA Physical Status Classification System | American Society of Anesthesiologists (ASA)https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system (accessed 9 May 2020).

3. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: The reality and challenges. *Journal of Microbiology, Immunology and Infection*. Epub ahead of print 2020. DOI: 10.1016/j.jmii.2020.03.034.

4. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020; 127: 104362.

5. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. *Gastroenterology*. Epub ahead of print April 2020. DOI: 10.1053/j.gastro.2020.03.065.

6. Minimal Standard Terminology | World Endoscopy Organization (WEO)http://www.worldendo.org/resources/minimal-standard-terminology-mst/ (accessed 3 April 2020).

Supplementary Table 2: Classification of endoscopic abnormalities

Chronic	Acute on Chronic abnormalities	Minor abnormalities	Major abnormalities
Barrett Esophagus	Any bleeding from Chronic abnormalities	Erythematous/Edematous mucosa *	Esophagitis
Duodenal Scalloping		Granular/Nodular mucosa	Pseudomembranous colitis
Colonic Melanosis		Candidosis / Candidiasis	Dielafoy lesion
Atrophic gastric mucosa			Erosions / Ulcers
Angiectasia			Mallory-Weiss tears
Ectopic gastric mucosa			Petechial/Hemorrhagic mucosa
Flat/Elevated or Excavated lesions / Polyps / Tumors			Erosed/Ulcerated mucosa
Esophageal varices			
Thickened/Enlarged gastric folds			
Ectopic pancreas			
Enlarged Brunners glands			
Hemorrhoids			
Condylomas			

* this category potentially includes aspecific minor abnormalities resulting from bowel cleansing regimens administered for lower GI tract endoscopies.

Supplementary Statement 3: Categorization of variables

Variables included in univariate/multivariate analysis were categorized as follows:

1. SEX: Male / Female
2. Pre-admission ASA score: ASA1 / ASA2 / ASA3 / ASA4 / ASA5
3. Comorbidities:
   a. Hypertension Yes / No
   b. Diabetes Yes / No
   c. Ischemic Cardiomyopathy Yes / No
   d. Atrial Fibrillation Yes / No
   e. Active Cancer Yes / No
   f. Cirrhosis Yes / No
   g. CKD Yes / No
   h. COPD / Asthma Yes / No
   i. Obesity Yes / No
4. Antiplatelet at admission: Yes / No
5. NSAIDS at admission: Yes / No
6. Anticoagulant at admission: Yes / No
7. GI symptoms:
   a. Any Yes / No
   b. Nausea Yes / No
   c. Abdominal Pain Yes / No
   d. Vomiting Yes / No
   e. Diarrhoea Yes / No
   f. Anorexia Yes / No
8. COVID respiratory disease: Yes / No
9. Hospital regimen: Intensive Care Unit (with invasive ventilation) / Sub-Intensive Care / Outpatient
10. Treatments during admission
    a. Antibiotics / Antimicotic Yes / No
    b. Antiviral Yes / No
    c. Hydroxychloroquine Yes / No
    d. Biologic therapy Yes / No
    e. Anticoagulation Yes / No
    f. Steroids Yes / No

Supplementary Table 3: Endoscopic procedures

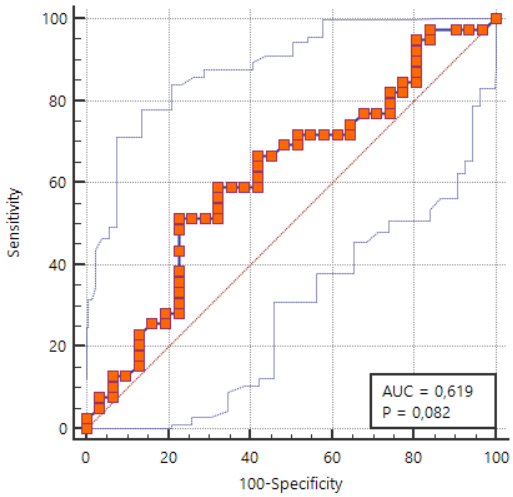
Characteristic	N = 114
Urgent, n (%)	76 (66.7%)
Indication	
Bleeding	63 (55.3%)
Upper GI Bleeding	41 (36.3%)
Lower GI Bleeding	22 (19.5%)
Other Symptoms	46 (40.6%)
Placement of Nutritional Device	5 (4.4%)
Exam	
Esophagogastroduodenoscopy	71 (62.3%)
Colonoscopy	27 (23.7%))
ERCP	10 (8.8%)
EUS	5 (4.4%)
Enteroscopy	1 (0.9%)
Median Onset-to-Endoscopy time, days [IQR]	13 [6-21]
Within 7 days from clinical onset	37 (32.5%)
After 7 days from onset	77 (67.5%)
Median Admission-to-Endoscopy time, days [IQR]	10.5 [5-21]
At Admission	9 (7.9%)
Within 7 days from admission	37 (32.5%)
After 7 days from admission	68 (59.6%)
Endoscopic Findings	
Major	52 (45.6%)
Acute on Chronic	13 (11.4%)
Minor	14 (12.3%)
Chronic	4 (3.5%)
Normal	31 (27.2%)

Supplementary Table 4: Categories of endoscopic finding according to type and timing of endoscopy

	Category of endoscopic finding			p-Value
	Major	Acute-on-Chronic	"Negative" procedures	
Type of Endoscopy				
Upper	40 (46%)	6 (6.9%)	41 (47.1%)	0.02
Lower	12 (44.4%)	7 (25.9%)	8 (29.6%)	
Timing of Endoscopy				
Median Onset-to-Endoscopy time, days [IQR]	13.5 [5.5-21]		15 [8.8-24.3]	0.2
Within 7 days from onset	19 (36.5%)		9 (18.4%)	0.04
Median Admission-to-Endoscopy time, days [IQR]	11 [5-21]		13 [5.3-23.8]	0.4
At admission	4 (7.7%)		3 (6.1%)	0.7
Within 7 days from admission	18 (34.6%)		14 (28.6%)	

Supplementary Figure 2:

Receiver Operating Characteristics Curve analysis of D-Dimers values distribution (ng/ml DDU) and their ability to discriminate between patients with Major abnormalities and patients with Minor, Chronic or no abnormalities. In the ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points of D-Dimers distribution. Each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular D-Dimers threshold. The best identified criterion was D-Dimer > 1850 ng/ml DDU.



D-Dimer > 1850 ng/ml DDU

Supplementary Table 5: Comparison between patients with Major abnormalities and Acute-on-Chronic findings

Characteristics	Major abnormalities N=52	Acute-on-Chronic findings N=12	p-Value
Male sex, n (%)	42 (80.8%)	8 (61.5%)	0.1
Median Age, years [IQR]	71 [62.5-79]	72 [56.3-73.8]	0.4
Age dico	19 (36.5%)		
Pre-admission ASA score, n (%)			0.1
ASA 1	6 (11.5%)	0	
ASA 2	20 (38.5%)	2 (15.4%)	
ASA 3	24 (46.2%)	10 (76.9%)	
ASA 4	2 (3.8%)	1 (7.7%)	
Comorbidities			
Hypertension, n (%)	30 (57.7%)	6 (46.2%)	0.5
Diabetes, n (%)	8 (15.4%)	4 (30.8%)	0.2
Ischemic Cardiomiopathy, n (%)	7 (13.5%)	3 (23.1%)	0.4
Atrial Fibrillation, n (%)	2 (3.8%)	2 (15.4%)	0.1
Active Cancer, n (%)	3 (5.8%)	1 (7.7%)	0.8
Cirrhosis	2 (3.9%)	4 (30.8%)	0.003
CKD	10 (19.2%)	1 (7.7%)	0.3
COPD / Asthma	7 (13.5%)	1 (7.7%)	0.6
Obesity	7 (13.5%)	1 (7.7%)	0.6
Antiplatelet			
Anticoagulant			
Median D-Dimer, ng/ml DDU [IQR]	2149 [567.8-3522.5]	2825 [1180-9829.5]	0.3
D-Dimer > 1850 ng/ml DDU	18 (48.6%)	5 (62.5%)	0.5
Median Onset-to-Endoscopy time, days [IQR]	13.5 [5.5-21]	5 [0.8-10.3]	0.02
Early Onset	19 (36.5%)	9 (69.2%)	0.04
Median Admission-to-Endoscopy time, days [IQR]	11 [5-21]	6 [1.8-9.8]	0.2
Symptoms, n (%)			
None	23 (46.9%)	6 (66.7%)	0.3
Nausea	9 (18.4%)	2 (22.2%)	0.8
Abdominal pain	17 (34.7%)	2 (22.2%)	0.5
Vomiting	9 (18.4%)	1 (11.1%)	0.6
Diarrhea	10 (20.4%)	1 (11.1%)	0.5
Anorexia	7 (14%)	0	0.2
COVID Respiratory Disease	42 (80.8%)	10 (76.9%)	0.8
Hospital Regimen			0.8
Intensive Care Unit, n (%)	18 (34.6%)	4 (30.8%)	
Sub-intensive Care, n (%)	34 (65.4%)	9 (69.2%)	
Treatments during admission			
Antibiotics / Antimicotic	42/49 (85.7%)	11/12 (91.7%)	0.6
Antiviral	26/47 (55.3%)	5/12 (41.7%)	0.4
Hydroxychloroquine	20/48 (41.7%)	6/12 (50%)	0.6
Biologic therapy	11/46 (23.9%)	2/12 (16.7%)	0.6
Anticoagulation	23/39 (59%)	4/10 (40%)	0.3
Steroids	13/49 (26.5%)	4/12 (27.3%)	0.6

Supplementary Table 6: Multivariate Logistic Regression

Variable	Odds Ratio *	p-Value
Atrial Fibrillation		0.259
Absent	1	
• Present	• 0.22 [0.02-3.05]	
D-Dimers value		0.013
≤ 1850 ng/ml DDU	1	
• > 1850 ng/ml DDU	• 12.12 [1.69-86.87]	
GI symptoms		0.035
Absent	1	
• Present	• 6.17 [1.13-33.67]	
Biologic Therapy		0.892
No	1	
• Yes	• 0.86 [0.09-7.91]	
Antiviral Therapy		0.083
No	1	
• Yes	• 0.23 [0.04-1.22]	

* adjusted for age, sex, pre-admission ASA score